IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

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| NOVOZYMES A/S,<br><br>Plaintiff,<br><br>v.<br><br>GENENCOR INTERNATIONAL, INC. and ENZYME DEVELOPMENT CORPORATION,<br><br>Defendants. | C.A. No. 05-160-KAJ |

**DEFENDANTS' OPPOSITION POST-TRIAL BRIEF**

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## I. INTRODUCTION

Novozymes apparently believes that the Court's task is to decide a post-trial motion for summary judgment—Novozymes contends that so long as it denies liability and says it has created a dispute of fact, it can stave off a judgment of non-infringement, invalidity, and unenforceability of the '031 Patent. Not so. While Novozymes denies that deceptive intent permeated its concealment of Machius '95, and denies its misrepresentations in and concerning the Borchert Declaration, for example, Novozymes' naked denials cannot explain away the pressing commercial circumstances surrounding prosecution of the '031 Patent, the "option" plan, and Novozymes' reliance on Machius '95 when it suited Novozymes' purposes, and concealment, when it did not. Long ago, Professor Wigmore explained the problem with Novozymes' approach:

> Human nature, and human actions governed and prompted by it, are such that *sometimes circumstances are more convincing than express testimony*, and it is no uncommon or infrequent occasion when Courts, in determining issues of fact, give weight to undeniable and established circumstances of the character indicated.

1 Wigmore on Evidence § 26 at 129 (3d ed. Supp. 1975) (emphasis added).

Considering all of the evidence, the inescapable conclusion is that Novozymes' arguments, and its witnesses, are not credible. Novozymes' reliance on half-truths and mischaracterizations in its Opening Post-Trial Brief only hammers that conclusion home.

## II. THE ALLEGED INVENTION OF THE '031 PATENT IS OBVIOUS

### A. Machius '95 Makes the Claimed Invention Obvious

Novozymes attempts to avoid the straightforward teachings of Machius '95 by asserting that it provides an unreliable structure and "tosses up" theories which it then rejects. (Novozymes' Post-Trial Brief at 31-32.) This argument is inconsistent with Novozymes' pre-litigation statements and the evidence at trial.

#### (1) Novozymes' Arguments Are Inconsistent With Its Pre-litigation Positions

Soon after Machius '95 published, Dr. Borchert invited Dr. Machius to give a talk at Novozymes. (Borchert, Tr. at 361:9-15, A-5592.) Dr. Borchert then incorporated Machius '95 into a talk that he gave

to the American Oil Chemists Society. (Borchert, Tr. at 361:16-362:19, A-5592–5593.) The '031 Patent inventors, including Dr. Borchert, relied on Machius '95 in a paper describing the structure of their chimeric alpha-amylase, comparing their structure with the features of the Machius '95 BLA structure. (TE 102 at 9100, A-8148.) They even took the unusual step of citing Machius '95 in the abstract, indicating a reference of high importance and relevance to their study. (Machius, Tr. at 782:2-783:11, A-6570–6571; TE 102 at 9099, A-8147.) (Genencor's Post-Trial Brief at 30; FF 86-90; CL 91-92.)

Most remarkably, Novozymes found the structure of BLA in Machius '95 so reliable that it cited this very structure as support for arguments before the PTO. In arguing for the patentability of claims in a different patent family before a different examiner (and prior to the launch of SPEZYME® Ethyl), Novozymes relied on the BLA structure taught in Machius '95 to make arguments to the PTO about the location in three-dimensional space of residues in BSG. (Borchert, Tr. at 364:22-365:1, A-5595–5596; TE 665 at NV-0094701, A-9065.) (Genencor's Post-Trial Brief at 30; FF 91-92; CL 91-92.)

Until Novozymes faced SPEZYME® Ethyl, it consistently took the position that Machius '95 provides important, accurate teachings about the three-dimensional structure of BLA relevant to BSG.

(2) Novozymes' Attacks Do Not Undermine the Clear Teachings of Machius '95

Machius '95 makes an explicit and unqualified statement:

> [Suzuki] Region I in BLA is a loop on the surface of domain B. This loop is enlarged in BAA by two extra residues, which could cause mobility of this region and a decreased thermostability of the whole protein.

(TE 173 at 553, A-8384.) (Genencor's FF 72.) None of Novozymes' criticisms today undermine the impact that this statement had on the protein engineer of ordinary skill in 1995 (or the impact that it would have had on Examiner Prouty, had Novozymes disclosed Machius '95 in the prosecution of the '031 Patent).

Novozymes' strategy is one of distraction. It avoids dealing with the explicit statement that Suzuki Region I is in a surface loop, instead arguing over theories of overall BLA structure. Machius '95 independently summarizes previous theories for the structural basis for the greater stability of BLA as

compared to BAN or BSG, and proposes its own.[1] (TE 173 at 553, A-8384.) Machius '95's teachings about Suzuki Region I are distinct from that discussion of the general bases for the higher stability of BLA. (Machius, Tr. at 784:16-21, A-6572; TE 173 at 553, A-8384.) (Genencor's Post-Trial Brief at 23-24; FF 70-74; CL 62.) When asked whether the debate over BLA thermostability raised by Dr. Arnold was important to the loop statement, Dr. Machius testified:

> No, it does not really matter whether calcium binding is increased or whether any other aspects are effected. What is important, to point out the underlying reason for these effects and that is simply the fact that this region is in a loop and it is shortened. (Machius, Tr. at 784:7-11, A-6572.)

Dr. Machius showed that a protein engineer of ordinary skill in 1995 would not have been confused by the explicit teachings of Machius '95. (Machius, Tr. at 472:21-473:7, A-5703–5704.) Novozymes presented no testimony at trial (or any evidence in the record) that a protein engineer would have been confused by or not understood the teachings of Machius '95 regarding Suzuki Region I being in a surface loop and the effect of that on thermostability.[2]

To create confusion, Novozymes contends that Machius '95 "takes back" the teachings about Suzuki Region I and thermostability. (Novozymes' Post-Trial Brief at 31.) This makes no sense. (Genencor's FF 79.) As Dr. Machius explained:

> The rejection referred to the prior art [theories]. Our own statement referred to just one minor aspect, one specific aspect, namely, the loop shortening that Suzuki observed. And we plainly pointed out that it is loop shortening that is responsible for increased thermostability. (Machius, Tr. at 784:16-21, A-6572.)

Novozymes further mischaracterizes Machius '95 by arguing that the paper acknowledges that the lack of structural information for BAA and the Suzuki mutants is "fatal" to the loop theory.

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[1] The post-filing date references discussed by Dr. Arnold at trial and cited by Novozymes in its Opening Post-Trial Brief (Novozymes' Post-Trial Brief at 32) are irrelevant to the question of obviousness, as it is axiomatic that obviousness is determined according to what one of ordinary skill in the art would have understood as of the effective filing date of the application, which, here, was in 1995. *See* 35 U.S.C. § 103 (defining the "prior art" as that available under 35 U.S.C. § 102, which does not include post-filing date references). *See, e.g., Velander v. Garner*, 348 F.3d 1359, 1377 (Fed. Cir. 2003).

[2] Novozymes' expert on X-ray crystallography and protein structure, Dr. Gideon Davies, was present throughout the trial but did not even take the stand to testify in response to Dr. Machius.

(Novozymes' Post-Trial Brief at 31.) Even a cursory reading of the relevant passage (TE 173 at 553, right column, A-8384) reveals that Machius '95 characterizes the lack of some structural information as merely an impediment to "completely judging" whether there are "special interactions" in Regions I and II of BLA, and not a "fatal flaw."[3]

Novozymes also argues that the alleged "problems" with the Machius '95 structure—lack of calcium, cleavage of the protein, lack of resolution, and unavailability of the atomic coordinates—make the structure highly questionable and undermine the conclusions stated in the paper.[4] (Novozymes' Post-Trial Brief at 6.) Novozymes misses the point—as the authors of Machius '95 (including a Nobel Prize winning crystallographer) did not feel the need to qualify their conclusion that Suzuki Region I is in a surface loop, a protein engineer would have understood that the authors drew their conclusion, and believed it to be valid, in light of the issues they themselves raised. (Machius, Tr. at 472:21-473:7, A-5703–5704.) (Genencor's FF 77-78, 80-82; CL 63.) After all, Dr. Borchert, his co-inventors, and Novozymes' expert did not find these supposed "flaws" so overwhelming when they incorporated discussion of Machius '95 into talks and scientific publications or relied on Machius '95 to support another Novozymes' patent application.

Finally, Novozymes asserts, incredibly, that Machius '95 does not actually disclose the structure of BLA. (Novozymes' Post-Trial Brief at 6.) Novozymes does admit, in a footnote, that Machius '95 provides a general description of the BLA structure, but claims that there is no "structure" disclosed because the article does not provide the atomic coordinates. Machius '95 does indeed disclose a great

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[3] Earlier in its brief, Novozymes attempts to undermine Machius '95 by misquoting this passage to say "cannot be judged because . . . " rather than "cannot be *completely* judged *by our study*, because . . . ." (*See* Novozymes' Post-Trial Brief at 7, lines 1-2; TE 173 at 553, A-8384.) The Court should not countenance this misleading tactic. *See Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476, 1486 (Fed. Cir. 1984).

[4] Novozymes relies on Dr. Machius' testimony at page 499, line 22 through page 500, line 15. (Novozymes' Post-Trial Brief at 6; Machius, Tr. at 499:22-500:15, A-5730–5731.) That testimony, however, relates only to the movement of the free ends of the cleaved region of the protein and does not support the assertion Novozymes makes. The only other evidence allegedly supporting this statement is paragraph 42 of Dr. Borchert's declaration in an unrelated interference. (TE 524, A-8903–8932.) This paragraph says that in 1996 one could not have predicted the topography of a calcium binding site from a structure that did not identify it. No credible stretch makes this cite support Novozymes' statement.

deal about the structure of BLA, including descriptions of specific portions of the molecule.[5] Protein engineers would not have needed the atomic coordinates to understand the explicit statement that Region I is in a loop (Machius, Tr. at 478:18-23, A-5709, 776:6-17, A-6564), and there was absolutely no evidence to the contrary.[6] (Genencor's FF 80-82; CL 63.)

Novozymes' attacks on Machius '95 exemplify its misunderstanding of the Court's task. Saying "we disagree" is not enough to defeat judgment after trial; attempting to do so with no evidence or mischaracterized evidence is even less effective.

(3) Machius '95 Provides a Reasonable Expectation of Success and Not Just an Invitation to Experiment

Novozymes argues that Machius '95 makes it only "obvious to try" to introduce the 179-180 deletion into BSG and does not provide the "reasonable expectation of success" required to make an invention obvious. (Novozymes' Post-Trial Brief at 27.) Novozymes misapprehends the controlling legal standard. The Federal Circuit, in its widely-cited discussion in *In re O'Farrell,* 853 F.2d 894, 903-904 (Fed. Cir. 1988), explains that "obvious to try" generally relates to two scenarios: (1) where the prior art offers parameters to vary or a wide variety of choices to try, without guidance as to which parameter or choice is likely to be successful; and (2) where the prior art discloses a new technology or general approach to explore, with only general guidance. Thus, what makes the difference between "reasonable expectation of success" and "obvious to try" is the level of guidance provided by the prior art. In

[5] Novozymes cites to Dr. Machius' testimony at page 454, lines 2-12 for the proposition that the coordinates are the structure. (*See* Novozymes' Post-Trial Brief at 6, n.2; Machius, Tr. at 454:2-12, A-5685.) This mischaracterizes Dr. Machius' testimony. He actually testified in that passage that the coordinates reflect a model of the three-dimensional structure in space. They were not the only description or model of that structure, though, as the numerous figures, charts, and teachings in Machius '95 make clear. (*See also* TE 173 at 548-554 Figs. 1-6, and 555 at Table 5, A-8379–8386.)

[6] No journals include atomic coordinates with the publication of the crystal structure, because of their volume. Delaying release of the coordinates is not uncommon—even Novozymes (including all three '031 Patent inventors) and its expert delayed release of coordinates in publications without qualifying structural statements (and the inventors did so, notably, while citing Machius '95 as evidence of BLA structure!). (Machius, Tr. at 777:7-781:18, A-6565–6569; TE 102, A-8147–8156.) (Genencor's FF 81 and 90.) No one testified at trial that a protein engineer would not have understood Machius '95's teachings about the loop structure including Suzuki Region I because the atomic coordinates were not included in or attached to the paper or immediately deposited in the Protein Data Bank.

addition, the standard does not require absolute certainty of success—just a "reasonable expectation." *Id.* *See also Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1166-67 (Fed. Cir. 2006) (finding that specific guidance provided "reasonable expectation of success" even when prior art indicated combination would work "sometimes").

Machius '95 provides far more specificity and guidance than any "obvious to try" scenario, giving clear direction that Suzuki Region I is a determinant of thermostability in BLA and that making the deletion in BAN increases its thermostability by virtue of shortening the loop. (Machius, Tr. at 472:12-20, A-5703; TE 173 at 553, A-8384.) (Genencor's FF 70-74, 84-85; CL 62-64.) The section entitled "Other bacterial α-amylases and thermostability" highlights the importance of understanding the molecular underpinnings of thermostability of the *Bacillus* alpha-amylases because industrial applications require them to be used at high temperatures. (TE 173 at 551, A-8382.) This section further states that BLA, BSG, and BAN are homologous and that their three-dimensional structures are expected to be similar. (TE 173 at 553, A-8384.) Machius '95 and Suzuki also both teach that unmodified BSG is already more thermostable than unmodified BAN (and, it follows that modification of BSG should result in an even more thermostable protein). (TE 115 at 18933, A-8233; TE 173 at 552, A-8383.) Thus, Machius '95 tells the protein engineer of ordinary skill what change to make—the deletion at 179 and 180—and in what enzyme to make it—BSG, in order to improve thermostability. (Machius, Tr. at 484:1-485:6, A-5715–5716, 774:3-22, A-6562; TE 173, A-8375–8390.) Guidance does not get more specific than this. (Genencor's Post-Trial Brief at 23-26; FF 68-74; CL 62, 64, 69.)

Novozymes attempts to undermine Machius '95 by attributing to Dr. Machius testimony that one could not have predicted from Machius '95 that the deletion would have resulted in stabilization. (Novozymes' Post-Trial Brief at 30.) Examining Novozymes' citation to the transcript (at 490:21-491:4, A-5721–5722) shows that these were its own lawyer's words, not Dr. Machius' testimony.[7] In addition,

[7] Dr. Machius answered counsel's question a bit cryptically—"one might have had to guess about the qualitative outcome, but certainly not about the magnitude,"—but later clarified in response to the question "in your opinion, could one have predicted that there would be some improvement," that "That's what I meant when I said qualitative." (Machius, Tr. at 508:15-23, A-5739.)

Novozymes ignores Dr. Machius' unequivocal testimony that, based upon Machius '95, a protein engineer would have expected the deletion to increase the thermostability of BSG—making the deletion in BSG would have been "a no-brainer." (Machius, Tr. at 774:3-775:18, A-6562–6563.)[8]

Dr. Arnold herself admitted that Suzuki provides the impetus to make the deletion in BSG. (Arnold, Tr. at 742:9-10, A-6530.) (Genencor's FF 167; CL 48.) Machius '95 adds to the motivation and confidence of a protein engineer by its structural teachings, providing clear guidance to make the Suzuki Region I deletion in BSG. Machius '95 is much more than just an invitation to experiment.

Of course, a protein engineer in 1995 would have had to make the deletion in BSG to know for certain what would be the result. (Arnold, Tr. at 742:7-12, A-6530.) This does not vitiate obviousness based on Machius '95. In *O'Farrell*, the Federal Circuit stated that "for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice," but confirmed this is not the standard for obviousness. *O'Farrell*, 853 F.2d at 903-904. *See also, Medichem*, 437 F.3d at 1166-67.

Novozymes agrees that absolute predictability is not required, as is shown in the '031 Patent itself. There, Novozymes disclosed and then claimed BSG or SEQ ID NO:3 with the 179-180 deletion without disclosing any working examples that were variants of BSG or SEQ ID NO:3. (TE 100 at cols. 31-40, A-7023–7027.) In claiming the BSG variants without any working examples, Novozymes represented to the PTO and the public in 1995 (only a couple of weeks after the Machius '95 publication) that results from making the deletion in alpha-amylases from other *Bacillus* species would have provided one of ordinary skill with a basis to conclude that the claimed invention would work in BSG—or else the '031 Patent is invalid. This is because under 35 U.S.C. 112, ¶ 1, a patent specification must, at the time

[8] Novozymes also cites to testimony from Dr. Zeikus (Zeikus, Tr. at 699:2-13, A-6107) as support for its contention that success was not reasonably expected. Dr. Zeikus did not really agree with Novozymes, however, testifying in the cited passage that Suzuki would have motivated one to make the deletion in BSG. Further, his testimony was based on the teachings of Suzuki alone, not Machius '95. As discussed in detail in Genencor's Opening Post-Trial Brief, Machius '95 provides strong additional assurance to those of ordinary skill in the art that the deletion would increase the thermostability of BSG. (Genencor's Post-Trial Brief at 20-26.)

of filing, provide a reasonable basis for one skilled in the art to conclude that the invention would work as alleged. *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322-24 (Fed. Cir. 2005). Novozymes cannot have it both ways—it cannot argue that Machius '95 and Suzuki do not render the claims obvious because the result was not absolutely predictable based upon the effects of the deletion in BAN, and yet rely on effects of the deletion in other *Bacillus* species for enablement of the alleged invention of the '031 Patent.

Again, Novozymes misses the point—it is not facing summary judgment, where a genuine dispute of material fact (not present here) might allow it to survive another day. Novozymes' quibblings with Machius '95 do not outweigh its clear, motivating teachings. Machius '95 renders obvious and invalidates claims 1, 3, and 5 of the '031 Patent.

B. **The Borchert Declaration Does Not Rebut the Obviousness of the '031 Patent**

Novozymes relies on the alleged unexpected results of the Borchert Declaration to rebut obviousness of the '031 Patent. Novozymes forgets that evidence of alleged unexpected results does not *per se* control the obviousness determination; it is "but a part of the 'totality of the evidence' that is used to reach the ultimate conclusion of obviousness." *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) (citations omitted). In this balancing, courts have often found that real unexpected results simply do not outweigh evidence that the prior art renders a claimed invention obvious. *See id.* at 1484 (holding that although unexpected results were supported by substantial evidence, they do not overcome the evidence that the claimed subject matter is obvious). In this case, even assuming *arguendo* that the results were truly unexpected, they do not outweigh the clear guidance and strong motivation provided by Machius '95 to make the BSG variants claimed in the '031 Patent. (Genencor's Post-Trial Brief at 21-22; CL 45-46, 65-67.)

But, the results here were not unexpected, legally or scientifically. Dr. Klibanov testified that improvements within the same order of magnitude as that observed in the prior art were not unexpected. (Klibanov, Tr. at 586:15-590:6, A-5817–5821.) Suzuki reports that making the 179-180 deletion in BAN resulted in a 25-fold improvement (Klibanov, Tr. at 589:20-590:6, A-5820–5821; TE 115 at 18937, Fig.

5, A-8237) In view of what Suzuki found and the differences in stability of the wild type enzymes under different conditions, improvement within an order of magnitude is what one of ordinary skill in the art would have expected in 1995. (Klibanov, Tr. at 589:20-590:6, A-5820–5821; TE 116, A-8239–8244; TE 117, A-8245–8250.) That the observed improvement may be commercially significant does not take away from the fact that it was expected. Dr. Borchert's results, which showed improvement in the same order of magnitude as shown in Suzuki, were just not scientifically unexpected to one of skill in the art, nor were they legally "unexpected," even if one could not have predicted the exact magnitude of the improvement in BSG. *See In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985) (holding that the fact that some compounds function more effectively and that the exact magnitude of the increased activity might not be predictable does not preclude a conclusion of obviousness). (Genencor's Post-Trial Brief at 21-22; FF 132-134; CL 53, 101.)

At most, the Borchert Declaration presented results that were different in degree, but not in kind, from the prior art. That is not enough. Taking the results most favorably to Novozymes, based on the evidence of record, the Borchert Declaration is insufficient to overcome the admitted *prima facie* obviousness of the '031 Patent. *See In re Merck & Co., Inc.*, 800 F.3d 1091, 1099 (Fed. Cir. 1986).[9]

### C. SPEZYME® Ethyl's Commercial Success and Genencor's Patent Application Do Not Outweigh the Hard and Fast Case of Obviousness Presented by Machius '95

Novozymes contends that other secondary considerations demonstrate that the claimed invention of the '031 Patent is not obvious. As with unexpected results, the law is clear that evidence of secondary considerations does not control *per se* the obviousness inquiry but, rather, must be balanced against the primary evidence of obviousness. In cases where the primary evidence of obviousness is strong, even unequivocal and legally relevant evidence of commercial success or other secondary factors will not outweigh the evidence of obviousness. *See Richardson,* 122 F.3d at 1484; *Ryko Mfg. Co. v. Nu-Star, Inc.*,

[9] In addition, the trial evidence made it clear that the Borchert Declaration and experiment were wholly unreliable, vastly exaggerated, and, at best, overstated the relative improvement, and for that reason do not rebut the obviousness of the '031 Patent. This subject is treated at length in Genencor's Opening Post-Trial Brief at pages 33-39 and below, regarding inequitable conduct (Section IV.B., *infra.*); to avoid repetition, the arguments are not restated here.

950 F.2d 714, 719 (Fed. Cir. 1991) (finding that evidence of long felt need, copying, and commercial success did not outweigh the primary considerations of obviousness); *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768-69 (Fed. Cir. 1989) (holding that, although record showed a highly successful product, the secondary considerations did not outweigh strong case of obviousness). Here, the primary considerations of obviousness are so strong that, even assuming that Novozymes had presented evidence of secondary considerations with the requisite nexus to the claimed invention, the invention claimed in the '031 Patent was obvious.

Critically, Novozymes bears the legal and factual burden of proving that there is a nexus between the alleged secondary considerations, such as the success of SPEZYME® Ethyl, and the advantages of the alleged invention of the '031 Patent. *See In re Paulsen,* 30 F.3d 1475, 1482 (Fed. Cir. 1994). Success of a product is only relevant in the obviousness determination if Novozymes can demonstrate that "the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang,* 100 F.3d 135, 140 (Fed. Cir. 1996). *See also McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed Cir. 2003) (finding district court properly discounted evidence of commercial success when advertising campaign obscured any potential nexus between merits of the product and commercial success); *Paulsen*, 30 F.3d at 1482.

Novozymes has not met its burden. Approximately nine years after Novozymes filed the '031 Patent application, Genencor launched SPEZYME® Ethyl. While SPEZYME® Ethyl has done well in the market, Novozymes' own documents and the testimony of its own witness shows that SPEZYME® Ethyl sold well because, at least: (1) it was cheaper than Novozymes' competing product Liquozyme SC (LeFebvre, Tr. at 621:14-23, A-6029; TE 507, A-8853–8856); (2) customers had positive, historic relationships with Genencor (and customers did not have such positive relationships with Novozymes) (TE 507, A-8853–8856); (3) customers wanted to maintain their relationships with Genencor to assure access to future technology (TE 507, A-8853–8856); and (4) Novozymes' bid for business from a major customer, RPBG, was too complicated. (TE 507, A-8853–8856.) Novozymes has not demonstrated that

it is the properties of the invention claimed in the '031 Patent, that are responsible for the commercial success of SPEZYME® Ethyl. Even assuming that SPEZYME® Ethyl falls within the asserted claims, Novozymes has not met its burden to prove the requisite nexus; the evidence of SPEZYME® Ethyl's commercial success cannot be considered against the obviousness of the '031 Patent.[10]

Novozymes also claims that Genencor customers demanded a "better" alpha-amylase than Genencor's products before SPEZYME® Ethyl came on the market, demonstrating a "long-felt need" for the invention of the '031 Patent. (Novozymes' Post-Trial Brief at 33.) Novozymes has hardly met its burden here, as the witness on whom it relies, Dr. Crabb, actually disagreed with Novozymes' assertions that Genencor's products before SPEZYME® Ethyl were "uncompetitive." (Crabb, Tr. at 46:14-21, A-5046, 48:14-20, A-5048.)

Finally, Novozymes makes much of a Genencor patent application (Novozymes' Pre-Trial Brief at 33), but one of the cases cited by Novozymes itself states that a defendant's filing of its own application is not dispositive on the patentability of the claims. *See Polaroid Corp. v. Eastman Kodak Co.*, 641 F. Supp. 828, 848 (D. Mass. 1985), *aff'd*, 789 F.2d 1556 (Fed. Cir.), *cert. denied*, 479 U.S. 850 (1986). This has been the law for years. *See Grefco, Inc. v. Kewanee Indus., Inc.*, 499 F. Supp. 844, 858 (D. Del. 1980) (finding that evidence of defendant filing its own patent "is entitled to very little, if any, weight on the issue of obviousness . . ." and that it "can not override overwhelming proof of obviousness under the . . . *Graham* test"); *Park-Ohio Indus., Inc. v. Letica Corp.*, 617 F.2d 450, 454 (6th Cir. 1980) (finding that application and prosecution of a patent by defendant did not constitute any type of admission of or estoppel as to nonobviousness of plaintiff's design in view of prior art).

Genencor's patent application is just more of the same. Like the evidence of alleged (but not proved) unexpected results and "long-felt need," and the alleged (but irrelevant) commercial success of SPEZYME® Ethyl, it is simply not sufficient to outweigh the strength of the prior art.

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[10] Only commercial success of products that fall within the claims in question is proper evidence of non-obviousness. *See In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). SPEZYME® Ethyl does not infringe any claim of the '031 Patent and, for this additional reason, its sales are not relevant secondary considerations that could rebut the admitted *prima facie* obviousness of the '031 Patent.

In sum, claims 1, 3, and 5 are invalid as obvious in view of Machius '95, as well as the combination of Suzuki and the Bisgard-Frantzen PCT. (Genencor's Post-Trial Brief at 21-22.)

## III. NOVOZYMES' NON-DISCLOSURES, MISREPRESENTATIONS, AND EGREGIOUS CONDUCT IN PROSECUTION RENDER THE '031 PATENT UNENFORCEABLE

### A. Novozymes Is Guilty of Inequitable Conduct by Concealing Machius '95

Even at this late hour, Novozymes continues to present new and incredible excuses to explain its failure to cite Machius '95 to the PTO during the prosecution of the '031 Patent. Accepting these new "justifications," which are totally rebutted by the evidence of record, would run afoul of time-honored rules:

> Undoubtedly, as a general rule, positive testimony as to a particular fact, uncontradicted by any one, should control the decision of the court; but that rule admits of many exceptions. There may be such an inherent improbability in the statements of a witness as to induce the court or jury to disregard his evidence, even in the absence of any direct conflicting testimony. He may be contradicted by the facts he states as completely as by direct adverse testimony; and there may be so many omissions in his account of particular transactions, or of his own conduct, as to discredit his whole story.

*Quock Ting v. United States*, 140 U.S. 417, 420-21 (1891). None of Novozymes' varying explanations for withholding Machius '95 hold water; all should be rejected.

#### (1) Novozymes Misrepresents to This Court Its "Consideration" of Machius '95

At trial, Mr. Garbell testified that he had not made a conscious decision about whether to cite Machius '95 during prosecution:

> Q. You knew that it had information, Machius '95 had information in it that it was not only different than Suzuki but information that Examiner Prouty might have wanted to know to decide what rejection she might put on over the art. Isn't that true?
>
> A. I did not have that consideration at the time. That's true.
>
> Q. You didn't even make a conscious decision whether to cite or not to cite Machius during this time frame; did you?
>
> A. That's correct. The information I had from reading it, as well as my discussions with two of the inventors and interference counsel, I never had any information before me which would even have led me to make that decision.

(Garbell, Tr. at 441:23-442:10, A-5672–5673.) Mr. Garbell also admitted that he could not fully evaluate materiality of the teachings of Machius '95 vis-à-vis the '031 Patent. (Garbell, Tr. at 443:7-15, A-5674.) In other words, at trial Mr. Garbell claimed innocence of even considering Machius '95 in connection with the '031 Patent prosecution.

Now, in its brief, Novozymes tries an entirely new and inconsistent story. Novozymes' Opening Post-Trial Brief intimates that Mr. Garbell and Dr. Borchert actually contemporaneously considered, but refrained from, submitting Machius '95 to the Examiner, because it was "fatally flawed." (Novozymes' Post-Trial Brief at 37.) This new story might have been credible had Novozymes heeded the following advice from the MPEP:

> [I]f information was specifically considered and discarded as not material, this fact might be recorded in an attorney's file or applicant's file, including the reason for discarding it. *If judgment might have been bad or something might have been overlooked inadvertently, a note made at the time of evaluation might be an invaluable aid in explaining that the mistake was honest and excusable.* Though such records are not required, they could be helpful in recalling and explaining actions in the event of a question of "fraud" or "inequitable conduct" raised at a later time.

MPEP § 2004, entitled "Aids to Compliance With Duty of Disclosure," at ¶ 18 (emphasis added). Mr. Garbell's testimony was exactly to the contrary.

The only "evidence" cited by Novozymes for Mr. Garbell's alleged thoughtful consideration of Machius '95 during the'031 prosecution is the declaration submitted by Dr. Borchert in connection with an interference concerning a different patent application, in which Dr. Borchert distinguished Machius '95 based on issues relating to calcium binding sites not relevant to the '031 Patent. (TE 524 at 13-14, A-8908–8909.) (Genencor's FF 91 and 94.) This supposedly proves that Dr. Borchert and Mr. Garbell decided not to disclose Machius '95 because of its "fatal flaws." Yet, Mr. Garbell testified that he never discussed with Dr. Borchert the relevance of Machius '95 to the '031 Patent, and that he never considered it in connection with the '031 Patent. (Garbell, Tr. at 442:5-21, A-5673.)

Novozymes' new story flies in the face of Mr. Garbell's testimony that he never gave thought to disclosing Machius '95 in the '031 Patent prosecution. This tale is not credible and should be rejected.

(2) Novozymes Misrepresents to This Court Its Alleged Concerns About the Reliability of Machius '95

Novozymes makes an eleventh-hour attempt to disavow its prior reliance on Machius '95. Novozymes now denigrates its teachings, in order to bolster the credibility of Mr. Garbell and Dr. Borchert regarding their non-disclosure of Machius '95. (Novozymes' Post-Trial Brief at 36-37.) Yet, Novozymes offers no meaningful rebuttal to the clarity of Machius '95 statements regarding Suzuki's Region I being within a surface loop, and that the disclosure in Machius '95 made it a "no-brainer" to make the Suzuki deletion in BSG. (Machius, Tr. at 774:3-22, A-6562.) Novozymes' arguments about the nature of Machius '95—that it is merely a description of a crystal structure rather than an engineered protein, and that it "does nothing more to help a protein engineer make and use the variants Suzuki already disclosed" (Novozymes' Post-Trial Brief at 36-37)—are red herrings: the crystal structure described by Machius '95 provides the structural basis for the stabilization observed by Suzuki, and, therefore, increased motivation and confidence in making the Suzuki deletion in BSG. (Genencor's Post-Trial Brief at 23-26.)

Until this case, Novozymes repeatedly relied on Machius '95 for the structure of BLA and what it meant for BSG. (*See* pp. 1-2, *supra*.) Novozymes' repeated pre-litigation citation to and reliance on Machius '95 puts the lie to its current claim that Machius '95 was or is "unreliable" and "immaterial." This story, too, should be rejected.

(3) Novozymes Usurped the PTO's Responsibility and Authority to Consider All of the Material Prior Art

Even if Mr. Garbell and Dr. Borchert did perceive Machius '95 to be "fatally flawed," it was up to the Examiner, not Novozymes, to decide whether it was relevant to patentability of the asserted claims. *See, e.g., LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066, 1076 (Fed. Cir. 1992). Mr. Garbell was well aware of the "when in doubt" rule of erring on the side of disclosure. (Garbell, Tr. at 431:19-432:5, A-5662–5663, 444:23-445:14, A-5675–5676.) (Genencor's FF 97; CL 92.) As the MPEP plainly states, "*the question of relevancy in close cases, should be left to the examiner and not the applicant*." MPEP § 2004, entitled "Aids to Compliance With Duty of Disclosure," at ¶ 10 (emphasis

added). This has been the law for years. *See, e.g., SCM Corp. v. Radio Corp. of Am.*, 318 F. Supp. 433, 449 (S.D.N.Y. 1970).

Novozymes' stories about Machius '95 beg a critical question: If Novozymes was so certain that Machius '95 was "fatally flawed," why did Novozymes not cite it and say so, and allow the Examiner to arrive at the same conclusion? Novozymes has offered no credible answer; to the contrary, Mr. Garbell conceded that the '031 Patent may not have issued had Machius '95 been cited (Garbell, Tr. at 445:9-14, A-5676) (Genencor's Post-Trial Brief at 31-33; FF 98; CL 90), a much more plausible reason for withholding Machius '95 than Novozymes' new "fatal flaw" story.

(4) Novozymes Had a Strong Motive to Act Inequitably

Novozymes had strong motivation to avoid additional rejections in view of the commercial pressures on Novozymes to carry out its option plan and obtain a patent "full speed" that would stop SPEZYME® Ethyl, which was out-competing Novozymes' product. (Borchert, Tr. at 377:24-378:25, A-5608–5609; LeFebvre, Tr. 620:21-22, A-6028; TE 516, A-8901–8902.) As Dr. Borchert's co-inventor, Dr. Bisgard-Frantzen, explained in an e-mail on which Mr. Garbell and Dr. Borchert were copied:

> This is a very complicated situation – but more relevant also a VERY important issue to deal with the best possible way, with the best experts involved. Termamyl SC is between top 5 of our most profitable products with a sale >100mio. Dkr, so it is worthwhile to do an extra effort.

(TE 110 at NV-0200004, A-8169 (emphasis in original).) (Genencor's FF 30-44; CL 94.)

These commercial pressures drove Dr. Borchert, who was concerned about Genencor, "our main competitor." (Borchert, Tr. at 355:8-356:15, A-5586–5587; TE 110 at NV-0200004, A-8169.) Once Dr. Borchert learned that SPEZYME® Ethyl contained the Suzuki deletion ("the two expected/feared amino acids") Dr. Borchert told his colleagues at Novozymes, including Mr. Garbell, that patent protection would be pursued "full speed" (Borchert, Tr. at 377:11-378:25, A-5608–5609; TE 516, A-8901–8902), so that SPEZYME® Ethyl could be removed from the market. (Genencor's FF 41-44; CL 94.)

In view of the mounting commercial pressures faced by Novozymes and the demonstrated high level of materiality of Machius '95, Novozymes' multiple, inconsistent, and continuously changing

explanations for its failure to cite Machius '95 are not credible. As in *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1420-22 (Fed. Cir. 1989) (appeal from D. Del.), Novozymes' knowledge of material prior art, combined with evidence of its surrounding actions and motivations, properly gives rise to an inference of deceptive intent, even though Novozymes denies it. Novozymes' assertion that Dr. Borchert and Mr. Garbell acted in "good faith" cannot be accepted. Novozymes acted with deceptive intent in not disclosing Machius '95. (*See also* section IV.C., *infra.*) (Genencor's Post-Trial Brief at 31-33; CL 79-87, 106-111.)

### B. Novozymes Is Guilty of Inequitable Conduct by Misrepresentations In and Concerning the Borchert Declaration

The key to issuance of the '031 Patent was the Borchert Declaration, which provided the "results" of an experiment allegedly comparing the relative improvement in BSG and BAN upon introduction of the Suzuki deletion. Even though Mr. Garbell designed the test expressly to "overcome" Suzuki, the conditions of the comparative tests of the Borchert Declaration were different from Suzuki in critical respects. These differences, together with data omissions and extrapolations, yielded an unreliable and highly exaggerated "improvement" in BSG relative to BAN. None of these facts were disclosed to the PTO, because Novozymes knew to do so would cost it the '031 Patent.

#### (1) The Borchert Declaration and Experiment Were Unreliable and Misleadingly Presented

Novozymes does not provide any convincing evidence which defends its manipulation of and misrepresentations about the underlying experiment, or that the results of the Borchert Declaration were reliable and accurate. Rather, Novozymes offers excuses (the "experiment showed what was really going on") and misrepresentations (BSG variant "does not just provide a similar improvement: it is very much better"). (Novozymes' Post-Trial Brief at 28 and 39.) All of Novozymes' excuses fail. And, rather than proving that the Borchert Declaration showed "what was really going on," Novozymes' most recent data establishes and confirms that the Borchert Declaration overstated the half-life of BAN WT, and thus the relative improvement in BSG vs. BAN.

(a) *The half-life of BAN WT was exaggerated*

Dr. Borchert knew or must have known that the conditions employed in his thermostability experiment would have resulted in an unreliable half-life for BAN WT that was greatly inflated due to the ramp-up period. (Klibanov, Tr. at 525:6-526:8, A-5756–5757; Borchert, Tr. at 26:17-22, A-5026.) (Genencor's Post-Trial Brief at 35; FF 108-115.) And, he plainly knew or must have known that these experimental conditions significantly differed from Suzuki, which Novozymes chose to "overcome" by alleged unexpected results. None of Novozymes' excuses for choosing, and not affirmatively disclosing, these different and biasing conditions is tenable.

(i) Excuse No. 1: The Genencor patent application

Novozymes submits that Dr. Borchert "used the same protocol as Genencor in its patent applications, for the same BSG variants," and that "Genencor does not use a pre-heated buffer either, for the same tests on the same enzymes." (Novozymes' Post-Trial Brief at 38, referring to Example 3 of Genencor's US 20060014265 A1; TE 202, A-8532.1–8532.46.) It is true that the disclosed method does not expressly teach preheating the buffer, but Novozymes ignores the fact that the application suggested use of the method for the BSG variants of Example 1 (TE 202 at 21-23, A-8532.21–8532.23), for which, due to their lengthy half-lives, the ramp-up period has very little, if any, effect. Such an approach is inappropriate for BAN WT, where the ramp-up period makes a significant contribution to the calculated half-life of the enzyme (Klibanov, Tr. at 604:7-605:9, A-6012–6013); the application did not suggest use of that method with BAN WT. In fact, Dr. Crabb's testimony established that Genencor might pre-heat the buffer in testing thermostability (Dr. Crabb was not asked about specific alpha-amylases). (Crabb, Tr. at 52:23-53:12, A-5052–5053.)

Similarly, while the cited procedure uses a comparable temperature to that used in the Borchert Declaration, it instructs the use of 5 mM calcium (TE 202 at 23, A-8532.23), 50 times greater than the amount used in the Borchert experiment. Borchert's calcium concentration (substantially lower than that taught in Suzuki) contributed to the instability of BAN WT in his "experiment" and the resulting unreliability of the BAN WT half-life calculation. (Genencor's FF 106.) Dr. Borchert stated at trial that

"if you have an alpha-amylase that is not sufficiently stable, you can somehow circumvent that by adding high levels of calcium." (Borchert, Tr. at 26:17-22, A-5026.) Dr. Borchert knew about the destabilizing effect of his low calcium concentration on BAN WT.

(ii) Excuse No. 2: The teachings of the '031 Patent

Novozymes would have the Court believe that the Borchert experiment followed the teachings of the '031 Patent. In particular, Novozymes asserts that the "experiment used an industrially-relevant low calcium concentration (0.1 mM) . . . as in the patent." (Novozymes' Post-Trial Brief at 38.) That calcium concentration was far, far lower than that of Suzuki, the prior art Novozymes chose to "overcome" and to which the declaration was directed. Novozymes cannot credibly explain why it neither followed the teachings of Suzuki nor disclosed to the Examiner the many differences between Dr. Borchert's expert and Suzuki. (Genencor's Post-Trial Brief at 33-36.)

And, Novozymes misrepresents it own patent. In support of its position that the '031 Patent teaches conducting a thermal inactivation test using 0.1 mM calcium, Novozymes cites to column 30, lines 62-67 of the '031 Patent. However, this refers to a section of the '031 Patent entitled "Determination of [alpha]-amylase Activity," which teaches conditions for the Phadebas enzyme activity assay rather than for the thermal inactivation step. As Dr. Klibanov explained, enzyme thermal inactivation tests such as those described in the Borchert Declaration entail heating an aqueous solution of the enzyme, periodically withdrawing samples from heat, and measuring their residual activity in an enzyme activity assay. (Klibanov, Tr. at 516:13-21, A-5747.) (Genencor's FF 102.) It is the heating step for which a calcium concentration of 0.1 mM is problematic. Once again, Novozymes employs half-truths to try to convince the Court of its "good intentions."

(iii) Excuse No. 3: Lack of preheating was "reasonable"

Novozymes argues that the "test buffer was not pre-heated, but this was reasonable with the thin test-tubes and pre-heated equipment that was used." (Novozymes' Post-Trial Brief at 39.) Novozymes plays fast and loose with the evidence to arrive at this conclusion. Novozymes cites to Ms. Holbo's testimony that the PCR machine in which the thermal inactivation tests are performed is preheated and

that the tubes in which the enzymes are placed are thin, and to Dr. Arnold's testimony that Genencor's patent application provides an example of an industrial protocol which does not disclose a preheating step. (Holbo, Tr. at 667:5-14, A-6075, 670:12-15, A-6078; Arnold Tr. at 750:17-21, A-6538, 753:12-20, A-6541.) However, as noted above, Genencor's application concerns alpha-amylases that are characterized by long half-lives whose measurement is not significantly, if at all, affected by a ramp-up period. (Klibanov, Tr. at 604:7-605:9, A-6012–6013.) None of the evidence to which Novozymes points supports the conclusion that it was reasonable to omit a preheating step for BAN WT, the only enzyme among the four tested by Dr. Borchert whose half-life calculation is significantly affected by a ramp-up period. (Klibanov, Tr. at 604:7-605:9, A-6012–6013; Crabb, Tr. at 52:23-53:12, A-5052–5053.)

(iv) Excuse No. 4: Ramp-up time was not "a real factor"

Novozymes relies on its recent experiments to sell the idea that "ramp-up time was not a real factor." (Novozymes' Post-Trial Brief at 39.) Again, Novozymes misleads: those very same experiments on which Novozymes relies, requested by its expert in response to Dr. Klibanov's observations that the BAN WT half-life calculation was inflated due to ramp-up (Arnold, Tr. at 749:1-19, A-6537), demonstrate the half-life of BAN WT to be approximately 0.435 minutes. This value is less than half the 0.9 minutes calculated by Dr. Borchert and much closer to Dr. Klibanov's calculation of approximately 0.3 minutes. (Arnold, Tr. at 765:8-25, A-6553.) The 0.435-minute half-life means that the improvement in BAN by making the Suzuki deletion is approximately 22-fold,[11] a value in line with the approximately 25-fold improvement observed in Suzuki's experiment. (Klibanov, Tr. at 545:15-549:7, A-5776–5780; TE 115 at Fig. 1, A-8234, Fig. 5, A-8237, 18935, A-8235.) Even putting aside the unreliability of the BSG del half-life calculation, these new data establish that there was at most a 2.4-fold to 3-fold relative improvement between the two enzymes, a far cry from Dr. Borchert's 5.7-fold (TE 508 at 4 ¶ 7, A-8860) and much closer to Dr. Klibanov's estimate of a 2-fold relative improvement. (Klibanov, Tr. at 549:5-8,

[11] Substituting 0.435 min for 0.9 min in the table below paragraph 7 at page 4 of the Borchert Declaration (TE 508, A-8857–8874) yields a BAN improvement of approximately 22x rather than Dr. Borchert's 11x.

A-5780.) This improvement is one of degree, not a change in kind, and was clearly not unexpected. (Klibanov, Tr. at 589:13-590:6, A-5820–5821.)

(b) *Novozymes omitted critical data points*

The half-life of BSG was exaggerated by omission of data points at 2881 and 2940 minutes.

(i) The data points at 2881 minutes

Novozymes asserts that the sample from which the residual activity measurements at 2881 minutes were taken had evaporated. (Novozymes' Post-Trial Brief at 39.) Rather than redoing the experiment per her usual practice (Holbo, Tr. at 669:9-12, A-6077), Ms. Holbo analyzed the residual activity of the sample and calculated its value as 56%. (Holbo, Tr. at 678:13-16, A-6086.) That value was lower than expected, which contradicts Novozymes' explanation for the omission of the 2881 data points; if the reading were bad due to evaporation, the value would have been higher than what was expected due to concentration of the enzyme solution. (Klibanov, Tr. at 537:5-17, A-5768.) (Genencor's Post-Trial Brief at 35-36; FF 125-128; CL 100.) Novozymes does not present any evidence to the contrary, and thus does not provide a valid explanation of why that residual activity value was excluded from the Borchert Declaration.

(ii) The valid data point at 2940 minutes

Ms. Holbo identically annotated three optical density ("OD") readings from the enzyme activity assay in the Borchert experiment, by placing them in parentheses: one of two readings at 20 minutes for BSG, another of two readings at 40 minutes for BSG, and one of two readings at 2940 minutes for BSG del. (TE 668, A-9097.) Ms. Holbo testified that these annotated readings were unreliable due to precipitate from the Phadebas enzyme activity assay. (Holbo, Tr. at 672:12-13, A-6080, 676:14-17, A-6084.) In the case of the two bad readings at 20 and 40 minutes for BSG, Dr. Borchert used the second reading from each time point in the Borchert Declaration; however, in the case of the reading at 2940 minutes for BSG del, Dr. Borchert discarded both readings, even the one Ms. Holbo testified was "fine." (Holbo, Tr. at 681:15-17, A-6089.) (Genencor's FF 129-131; CL 100.)

It is Novozymes' position that the "fine" data point at 2940 minutes was discarded because it exhibited a "wildly" different reading from its counterpart. (Novozymes' Post-Trial Brief at 39.) However, because the bad reading resulted from excess blue dye rather than an aberrant activity of the enzyme, the good counterpart should not have been discarded, no matter how far apart the good and bad data points were. Indeed, Dr. Klibanov found no reason for Dr. Borchert's omission of the valid data point. (Klibanov, Tr. at 538:7-10, A-5769.) The effect of the omission was an overestimation of the relative improvement of BSG vs. BAN as a result of the Suzuki deletion. (Klibanov, Tr. at 540:9-14, A-5771.) Dr. Arnold testified that the improvement in the half-life of BSG is 55-fold instead of 63-fold if the good data point is factored into the calculation (Arnold, Tr. at 760:17-25, A-6548), lowering the relative improvement even further. (Genencor's FF 116-120, 131.)

(c) *Novozymes improperly extrapolated the half-life of BSG del*

In addition to omitting multiple data points from the BSG del half-life calculation, Novozymes presented the Examiner with an extrapolated half-life for BSG del, even though there were no experimental measurements or data to justify the extrapolation. (Klibanov, Tr. at 532:6-9, A-5763; 533:20-534:5, A-5764–5765.) Novozymes' litigation testing of BAN WT demonstrates that thermal inactivation of that enzyme does not obey first order kinetics, making extrapolation improper. (Klibanov, Tr. at 532:6-9, A-5763.) If, like BAN WT, BSG del does not obey first order kinetics, the extrapolated BSG del half-life is unreliable. As a result, the Borchert Declaration may have overestimated the relative improvement of BSG versus BAN upon introduction of the Suzuki deletion. (Klibanov, Tr. at 534:16-535:2, A-5765–5766.) (Genencor's Post-Trial Brief at 36; FF 116-120; CL 101.) Novozymes did not present any evidence to the contrary.

(2) Novozymes' Misrepresentations Are Material

Were the misrepresentations of the Borchert Declaration material? Undoubtedly so: the Examiner provided the following reasons for allowance of the '031 Patent:

> While claims 48 and 50-52 would appear to be prima facie obvious over Suzuki et al. (JBC 260:6518, 1989) in view of Bisgard-Frantzen *et al.* (WO95/10603) as explained in the rejection of previous claims 30-33, 35 and 37-39 in the Office Action mailed,

> 7/29/03, *the declaration of Dr. Torben Borchert submitted 9/7/04 establishes that the claimed variants exhibit unexpected large increases in thermostability when compared to the increases in thermostability obtained for the corresponding mutations taught by Suzuki et al.* As such the claimed variants are non-obvious over the prior art.

(TE 101 at 756, A-7796 (emphasis added).)

Not only did the Examiner expressly rely on Novozymes' misrepresentations and omissions, those very same misrepresentations and omissions concealed information inconsistent with Novozymes' claim of "unexpected" results, and were therefore material as a matter of law. *See Digital Control Inc. v. Charles Machine Works*, 437 F.3d 1309, 1318-19 (Fed. Cir. 2006) (reviewing standards of materiality). Time and again, this Court, and courts facing similar circumstances in which patentees withheld "bad data" from the PTO and/or mischaracterized seemingly good data, have found that such omissions material. *See Grefco*, 499 F. Supp. at 864-69 (finding that inventors' "doubts" concerning omitted test results did "not excuse their failure to apprise the Examiner of the results . . ." and that this omission, together with selectively presenting and misrepresenting "favorable" results constituted inequitable conduct) (citing *In re Multidistrict Litig. Involving Frost Patent*, 540 F.2d 601, 609-10 (3d Cir. 1976) (finding inequitable conduct based on withheld experiments and mischaracterizations in affidavit submitted to PTO)); *Monsanto Co. v. Rohm & Haas Co.*, 456 F.2d 592, 597-600 (3d Cir. 1972) (stating that a reading of the affidavit, which failed to include negative experiment results, "permits, if not compels, the misleading inference that it constituted a complete and accurate analysis of all the testing instead of an edited version thereof. Concealment and nondisclosure may be evidence of and equivalent to a false representation, because the concealment or suppression is, in effect, a representation that what is disclosed is the whole truth." (citations omitted)). *See also Cosden Oil & Chem. Co. v. American Hoechst Corp.*, 543 F. Supp. 522, 547-48 (D. Del. 1982); *CPC Int'l, Inc. v. Standard Brands Inc.*, 385 F. Supp. 1057, 1067-69 (D. Del. 1974); *SCM*, 318 F. Supp. at 448-50; *Shelco, Inc. v. Dow Chem. Co.*, 322 F. Supp. 485, 517 (N.D. Ill. 1970). (Genencor's Post-Trial Brief at 36-37; CL 106-111.)

Just as telling, while Novozymes emphasized to Examiner Prouty it was producing unexpected results to overcome the rejection based on Suzuki, it never called to her attention the differences between

the Borchert experiment and that of Suzuki. Why not? The answer is clear from the Reasons for Allowance, cited above: Examiner Prouty believed Dr. Borchert had shown unexpected results "compared to the increases in thermostability obtained for the corresponding mutations taught by Suzuki, *et al.*" (TE 101 at 756, A-7796.) It would obviously have mattered to Examiner Prouty that the conditions chosen by Novozymes differed from Suzuki's and biased the results. (Genencor's FF 45-48.) Thus, Novozymes' omission was highly material.

(3) Novozymes Acted With Deceptive Intent

Unfortunately (for Genencor), Novozymes had every reason not to act in good faith: Novozymes was under pressure to obtain a patent that would knock SPEZYME® Ethyl off of the market. (Borchert, Tr. at 377:24-378:25, A-5608–5609; LeFebvre, Tr. 620:21-22, A-6028; TE 516, A-8901–8902.) When Novozymes submitted the Borchert Declaration to the PTO, the '031 Patent application was about a month away from the non-extendable deadline for responding to the Office Action dated April 6, 2004. (TE 101 at 695, A-7735; TE 508, A-8857–8874). *See* 35 U.S.C. § 133 (setting a statutory limit on the period with which a response must be filed). Novozymes had to ensure success of its "option" plan by securing allowance of its application by that deadline if it were to avoid a final rejection. Once the Examiner issued a final rejection, Novozymes would have been precluded from broadening its claims or submitting the results of comparative testing, its only recourses being a lengthy appeal (MPEP § 1204; 35 U.S.C. § 134) or continued prosecution (MPEP § 706.07(h); 37 C.F.R. § 1.114). Neither of these scenarios would allow Novozymes to proceed with the "full speed" mandated by Novozymes' plan to remove SPEZYME® Ethyl, a highly successful product of its "main competitor," Genencor, from the marketplace. (Borchert, Tr. at 355:8-356:15, A-5586–5587, 377:24-378:25, A-5608–5609; TE 110 at NV-0200004, A-8169.) (Genencor's FF 41-44.)

Novozymes did not present any credible evidence to justify its highly material misrepresentations made at a time it had strong commercial motives and faced intense pressure to secure issuance of the '031 Patent. Culpable, deceptive intent can be inferred clearly and convincingly from the totality of the evidence here:

> In contrast to cases where allegations of fraud are based on the withholding of prior art, there is no room to argue that submission of false affidavits is not material. . . . It cannot be said that these misrepresentations to the PTO were the result of an honest mistake. *Cf. Norton v. Curtiss*, 433 F.2d 779, 794, 167 USPQ 532, 544 (C.C.P.A. 1970). While direct proof of intent to mislead is normally absent, such submissions usually will support the conclusion that the affidavit in which they were contained was the chosen instrument of an intentional scheme to deceive the PTO.

*Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1570-71 (Fed. Cir. 1983). (Genencor's Post-Trial Brief at 37-39.)

### C. Novozymes' Pattern of Misrepresentation and Concealment Compels the Conclusion that It Acted Inequitably

The evidence clearly and convincingly establishes that the Examiner allowed the claims of the '031 Patent as a direct result of Novozymes' intentional misrepresentations regarding the "very surprising" and "unexpected" nature of the results of the Borchert Declaration as compared to the results shown in Suzuki, and the intentional nondisclosure of Machius '95. Novozymes' persistent pattern of material misrepresentations, including omissions and half-truths to the PTO, is tantamount to clear and convincing evidence of deceptive intent. *See PerSeptive Biosystems, Inc. v. Pharmacia Biotech., Inc.*, 225 F.3d 1315, 1320 (Fed. Cir. 2000). (Genencor's CL 79-86.)

Fundamentally, Novozymes took advantage of a busy patent examiner to obtain a patent without proper disclosure of the closest prior art and full consideration of the experimental conditions and all of the data underlying the claim of "unexpected results." The duty of candor, including the "when in doubt" rule, exists because "[a] patent examiner is not equipped to make independent examinations. Of necessity, he must accept representations made to him unless he has before him something which questions the validity of those representations." *CPC Int'l*, 785 F.Supp. at 1067. As Mr. Garbell admitted, attorneys in particular have the duty to assure that when an applicant chooses to rely on unexpected results, all the appropriate data, both good and bad, are before the examiner. (Garbell, Tr. at 444:23-445:3, A-5675–5676.) *See* MPEP § 716.01(d), 716.02(b), 716.02(d); *In re Frost*, 540 F.2d at 609-11 ("Again, General's attorneys should not have allowed this statement [alleged "markedly superior results"] to go to the examiner without some indication that data existed casting doubt on the correctness

of [defendant's] expectations."). Mr. Garbell's failure to make any inquiry about the data assured that he would breach this duty, as he did. (Genencor's FF 97; CL 88-92.)

And, the duty of disclosure includes not only test data underlying experiments, but also how alleged unexpected results compare to the closest known prior art:

> Where, as here, an applicant attempts to overcome a rejection by submitting a comparative showing of properties, the very act of submitting that showing, apart from what is represented therein, must also be regarded as a representation. The most meaningful comparison, in such instances, would be that between the claimed invention and the best embodiment of the prior art available. *Therefore, in submitting evidence of comparative tests, unless the circumstances indicate the contrary, an applicant must be held to be representing that his showing includes a fair and accurate demonstration of the closest prior art of which he is aware.*

*In re Frost*, 540 F.2d at 611, n.35 (citing *Norton v. Curtiss*, 433 F.2d at 794) (emphasis added).

There were no circumstances to the contrary here. Novozymes told the PTO it was presenting results that were "unexpected" and "very surprising" compared to Suzuki (reaching out to "overcome" a prior art rejection no longer pending, in fulfillment of the "option" plan). But, critically and deceptively, Novozymes did not tell the PTO there was closer prior art, Machius '95, and did not call to the PTO's attention the many and significant differences between the Borchert experiment and the basis for comparison, Suzuki. Mr. Garbell's testimony as to what would have happened had Machius '95 been disclosed and the Examiner's Reasons for Allowance make it clear that these omissions were misleading, material, and intentional. (Genencor's FF 45-48, 92-101; CL 88-105.)

This Court quite properly tolerates no excuses when the duty of candor has been breached. Not even the time-tested refrain of "blame the attorneys" will excuse an applicant's failure to disclose to the PTO, as Novozymes' predecessor and counsel know well:

> [N]ovo asks us to hold, on the one hand, that the failure of Dr. Christensen and his co-inventors to disclose the truth about Example 1 to Novo's attorneys absolves them of their duty to disclose this information to the PTO or the Board, because without their attorney's consultation, they could not have known that this information was material. At the same time, Novo asks us to hold that its counsel's failure to disclose the truth about Example 1 to the PTO or Board is excused because the inventors failed to fully inform them of the details surrounding Example 1. As we have done in similar situations in the past, we reject the "circular logic" of this request. *See Braessler*, 267 F.3d at 1380 ("We refuse to pursue the circular logic of Braessler's request and decline to carve out an exception to the inequitable conduct law to shield those guilty of inequitable conduct

> from responsibility for their actions."); *see also Molins*, 48 F.3d at 1178 (stating that the knowledge and actions of an applicant's representatives are chargeable to the applicant (citing *FMC Corp.*, 835 F.2d at 1415 n.8)). Accordingly, the district court correctly concluded that Novo knew or should have known that the PTO and the Board would have considered the information relating to Example 1 important in evaluating whether the 1983 PCT application was enabled.

*Novo Nordisk Pharms., Inc. v. Bio-Technology Gen. Corp.*, 424 F.3d 1347, 1361-62 (Fed. Cir. 2005).

This Court has consistently applied the same high standard:

> Judge Wright was concerned with this problem in *Corning Glass Works v. Anchor Hocking Glass Corp.*, 253 F.Supp. 461 (D. Del. (1966)):
>
> 'Even though misrepresentations made to the Patent Office are not legally material to the issuance of a patent, nevertheless, this Court, being a court of equity, can and should refuse to enforce the patent if the Court finds the patentee made intentional misrepresentations to the patent examiner. *i.e.*, if the patentee came into the court with unclean hands. The proceeding before the patent examiner is ex parte and an examiner has no way, in many cases, to ascertain the truthfulness of the representations made to him. Necessarily he must rely on the good faith of the applicant. Absolute honesty and good faith disclosure is necessary.'
>
> I agree with this statement. It fits the present case. *No one can tell with* certainty *what would have happened if [the patentee] had dealt fairly with the Patent Office. But the fact remains that [the patentee] did withhold relevant facts. Which side in this litigation is to suffer from this conduct? It is appropriate that it should be [the patentee] who suffers.* Any other rule would fail adequately to discourage conduct of this sort merely because of the circumstance, which must be present in many cases, that it turns out to be impracticable to ascertain what the Examiner, who did not know the true facts, would have done if he had known them. The evidence here justifies the conclusion that this court should not enforce a patent obtained under these circumstances. I so hold.

*CPC Int'l, Inc. v. Standard Brands Inc.*, 385 F. Supp. 1057, 1068 (D. Del. 1974) (quoting *SCM Corp. v. Radio Corp. of Am.*, 318 F. Supp. 433 (S.D.N.Y. 1970) (quoting *Corning Glass Works v. Anchor Hocking Glass Corp.*, 253 F.Supp. 461, 470 (D. Del. 1966) (Wright, J.)) (emphasis added).

In the end, the Court knows what would have happened had Novozymes been honest with the PTO. Mr. Garbell admitted that the '031 Patent might not have issued had Novozymes' disclosed Machius '95. Had the manifold deficiencies and misleading statements in and concerning the Borchert Declaration been disclosed as well, all hope for the '031 Patent would have been lost—it would not have issued then, or ever. The Court should not enforce a patent obtained in such circumstances.

### D. Novozymes' Manipulation of the Prosecution Renders the '031 Patent Unenforceable Due to Prosecution Laches

The asserted claims of the '031 Patent issued approximately ten years after the earliest effective filing date. In the end, Novozymes intentionally delayed prosecution of the '031 Patent (what else is "buying time" and asserting straw-man claims?), disingenuously narrowing the claims to permit it time to obtain broad claims, which, like those it had surrendered, were targeted at Genencor and the Suzuki deletion in SPEZYME® Ethyl. Unaware of the "option" plan, Genencor invested in and launched SPEZYME® Ethyl in April 2004, only to face this baseless lawsuit.

Thus, the Court should also find that the '031 Patent is unenforceable due to prosecution laches. While the doctrine is not often applied, egregious conduct that delays prosecution to the detriment of the public (including competitors) properly gives rise to a finding of prosecution laches, *see Intuitive Surgical, Inc. v. Computer Motion, Inc.*, No. Civ.A. 01-203-SLR, 2002 WL 31833867, at *3 (D. Del. Dec. 10, 2002), especially where, as here, the patent applicant engaged in unusual steps to delay prosecution, *see Reiffin v. Microsoft Corp.*, 281 F. Supp. 2d 1149, 1151-52 (N.D. Cal. 2003), resulting in a broadening of claims. *See MOSAID Techs. Inc. v. Samsung Elecs. Co.*, 362 F. Supp. 2d 526, 553 (D.N.J. 2005). Notwithstanding Novozymes' assertion that it technically complied with the statutes and rules in prosecuting the '031 Patent (which is false, given Novozymes' demonstrated inequitable conduct), the '031 Patent is unenforceable because of the unreasonable and unexplained delay in prosecution resulting from Novozymes' dilatory prosecution, exacerbated by the purposefully manipulative "option" plan. *See Symbol Techs., Inc. v. Lemelson Med.*, 277 F.3d 1361, 1363-68 (Fed. Cir. 2002). (Genencor's CL 112-114.)

## IV. SPEZYME® ETHYL DOES NOT INFRINGE PROPERLY CONSTRUED CLAIMS 1, 3, AND 5 OF THE '031 PATENT

### A. Overview of Claim Construction and Non-infringement

Genencor does not infringe the '031 Patent if its claim constructions are adopted by the Court. Considering the asserted claims in reverse order for convenience of explanation only:

First, if the Court adopts *either* of Genencor's proposed constructions of "parent *Bacillus stearothermophilus* alpha-amylase," SPEZYME® Ethyl does not infringe claim 5 because: (i) under both constructions, the "reference" alpha-amylase to which SPEZYME® Ethyl is compared has 514 or 515 amino acids; (ii) SPEZYME® Ethyl has only 484 amino acids; and (iii) the limiting "consists of" transitional phrase in claim 5 permits the 179-180 deletion (using SEQ ID NO:3 for numbering) as the only difference between SPEZYME® Ethyl and the 514 or 515 amino acid "reference" alpha-amylase. SPEZYME® Ethyl lacks about 30 amino acids as compared to a 514 or 515 amino acid alpha-amylase, so there is no literal infringement. (Genencor's Post-Trial Brief at 18-19.) (Genencor's CL 31-34, 37-38.)

Second, if the Court adopts Genencor's construction of "% homology," SPEZYME® Ethyl does not infringe claim 3 because: (i) the "reference" alpha-amylase to which SPEZYME® Ethyl is compared is SEQ ID NO:3; (ii) SEQ ID NO:3 differs from SPEZYME® Ethyl in 5 amino acids throughout the body of the protein plus 30 amino acids from the C-terminus of SEQ ID NO:3; and (iii) using any appropriate method for calculating % homology that accounts for all substitutions, insertions, and deletions, SPEZYME® Ethyl does not have "at least 95% homology" to SEQ ID NO:3, such that claim 3 is not literally infringed. (Genencor's Post-Trial Brief at 17-18; CL 29-30.)

Third, if the Court adopts *either* of Genencor's proposed constructions of "parent *Bacillus stearothermophilus* alpha-amylase," as well as Genencor's construction of "% homology," SPEZYME® Ethyl does not infringe claim 1 because: (i) the "reference" alpha-amylase to which SPEZYME® Ethyl is compared has 514 or 515 amino acids; (ii) SPEZYME® Ethyl has only 484 amino acids; and (iii) using any appropriate method for calculating % homology that accounts for all substitutions, insertions, and deletions, SPEZYME® Ethyl does not have "at least 95% homology" to any alpha-amylase having 514 or 515 amino acids. Claim 1 is not literally infringed. (Genencor's Post-Trial Brief at 16-18; CL 21-26.)

### B. Novozymes' Construction of "Parent *Bacillus stearothermophilus* Alpha-amylase" Is Incorrect and Fatal to Novozymes' Infringement Case

Even though Novozymes independently construes "parent" and "*Bacillus stearothermophilus* alpha-amylase," the terms must be taken together to arrive at a proper construction of "parent *Bacillus*

*stearothermophilus* alpha-amylase." Novozymes' proposed construction does not withstand scrutiny for several reasons.

Novozymes defines "parent" as an antecedent protein that is altered to provide a "variant" protein (Novozymes' Post-Trial Brief at 16), and concludes that the "parent" is "an unaltered protein that is modified by the deletion, substitution, or insertion of amino acids to make a variant protein." (Novozymes' Post-Trial B rief at 17.) Novozymes' construction requires that there be at least one deletion, substitution, or insertion of an amino acid into or from the "parent" to make a variant, necessarily implying that the variant is derived from the parent. (Alber, Tr. at 202:8-11, A-5203; Arnold, Tr. 138:8-9, A-5139.) (Genencor's FF 15.) That construction encompasses sequence changes resulting from genetically engineering the DNA encoding the parent (Alber, Tr. at 202:12-19, A-5203; Arnold, Tr. at 137:19-139:17, A-5138-5140) as well as sequence changes resulting from other processes, such as post-translational modifications. (Alber, Tr. at 204:4-206:2, A-5205-5206; Arnold, Tr. 176:19-177:13, A-5177-5178.) (Genencor's FF 17 and 19.) Yet, Novozymes' construction is incomplete because it ignores the testimony of its own inventor and expert that the "parent" must be a wild type alpha-amylase. (Borchert, Tr. at 22:16-23:1, A-5022–5023, 23:9-24:4, A-5023–5024; Arnold, Tr. 137:19-138:25, A-5138-5139, 139:22-24, A-5140, 144:13-20, A-5145, 177:14-19, A-5178, 179:15-25, A-5180.) (Perhaps that is what Novozymes means in its construction when it characterizes a "parent" as an "unaltered" protein.)

Novozymes construes "*Bacillus stearothermophilus* alpha-amylase" to mean the functional enzyme that is "actually produced" by "the" alpha-amylase gene from a *Bacillus stearothermophilus* organism (*i.e.*, bacterium). (Novozymes' Post-Trial Brief at 18.) Again, there is no mention that the *Bacillus stearothermophilus* is a wild type organism.

Reading these terms together (but ignoring the admission that the parent is a "wild type"), Novozymes construes the phrase "parent *Bacillus stearothermophilus* alpha-amylase" to mean the functional enzyme that is "actually produced" by the alpha-amylase gene from a *Bacillus stearothermophilus* organism from which the variant was derived. That construction is incorrect.

(1) Novozymes' Construction Is Inconsistent With the '031 Patent and File History

(a) *The patent and file history dictate that "parent Bacillus stearothermophilus alpha-amylase" means "an alpha-amylase having the amino acid sequence of SEQ ID NO:3"*

The Examiner's and Novozymes' statements during prosecution of the '031 Patent show that they both considered the noted claim language to mean "an alpha-amylase having the amino acid sequence of SEQ ID NO:3." For a detailed explanation why the intrinsic record dictates that construction ("Genencor's Construction"), *see* Genencor's Opening Post-Trial Brief at 5-8.

(b) *Novozymes' construction analysis ignores key portions of the '031 Patent*

Novozymes avoids the very passages of the '031 Patent that expressly define "parent *Bacillus stearothermophilus* alpha-amylase" as having the amino acid sequence of SEQ ID NO:3. Not surprisingly, those passages are inconsistent with Novozymes' hoped-for construction. The '031 Patent provides several explicit definitions of "parent alpha-amylase," including the following, which are totally ignored in Novozymes' analysis:

> Accordingly, in a first aspect the present invention relates to variants of a parent α-amylase, the parent α-amylase in question being one which:
>
> i) has one of the amino acid sequences shown in SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 7, respectively, herein; or
>
> ii) displays at least 80% homology with one or more of the amino acid sequences shown in SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 7; and/or displays immunological cross-reactivity with an antibody raised against an α-amylase having one of the amino acid sequences shown in SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 7, respectively; and/or is encoded by a DNA sequence which hybridizes with the same probe as a DNA sequence encoding an α-amylase having one of the amino acid sequences shown in SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 7, respectively.

(TE 100 at col. 3:25-42, A-7009 (emphasis added).) Note that each definition of a parent alpha-amylase in that quotation refers to four sequences of the sequence listing, and only one of those, SEQ ID NO:3, is a *Bacillus stearothermophilus* alpha-amylase. The other sequences, SEQ ID No. 1, SEQ ID No. 2, and SEQ ID No. 7, refer to alpha-amylases of alkalophilic *Bacillus* strains NCIB 12512 and NCIB 12513 and a *Bacillus* sp. #707, respectively. (TE 100 at col. 7:24-40, A-7011.)

In addition, the '031 Patent contains the following discussion under the highly relevant heading, "The Parent α-amylase," which is also ignored in Novozymes' analysis:

> As already indicated, an α-amylase variant of the invention is very suitably prepared on the basis of a parent α-amylase having one of the amino acid sequences shown in SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 7, respectively (vide infra). . . . The parent α-amylases having the amino acid sequence shown in SEQ ID No. 3 is obtainable from *Bacillus stearothermophilus* and is described in, inter alia, *J. Bacteriol.* 166 (1986) pp. 635-643. . . . Apart from the variants of the above-mentioned parent α-amylases having the amion acid sequences shown in SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 7, respectively, other interesting variants according to the invention include variants of parent α-amylases which have amino acid sequences exhibiting a high degree of homology, such as at least 70% homology, perferably (as already indicated) at least 80% homology, desirably at least 85% homology, and more preferably at least 90% homology, e.g., 95% homology, with at least one of the latter four amino acid sequences.

(TE 100 at col. 7:19-51, A-7011 (emphasis added).) In view of these statements, the recitation of "parent *Bacillus stearothermophilus* alpha-amylase" in claims 1 and 5 means a "parent alpha-amylase from the species *Bacillus stearothermophilus* having SEQ ID NO:3," as opposed to a parent alpha-amylase of any of the other *Bacillus* species having either SEQ ID No. 1, SEQ ID No. 2, or SEQ ID No. 7.

Curiously, despite these explicit definitions of "parent alpha-amylases" in the '031 Patent, none are even mentioned in Novozymes' brief. There is over a page of discussion construing "parent" that references no less than *fifteen* other passages in the '031 Patent,[12] none of which is nearly as explicit as those quoted above. What would motivate Novozymes to ignore the most "on point" definitions in the '031 Patent? The only reasonable answer is that it wants to avoid referencing those portions quoted above because they explicitly define "parent" to mean four amino acid sequences, only one of which—SEQ ID NO:3—is a *Bacillus stearothermophilus* alpha-amylase.

This approach is improper. The Federal Circuit has affirmed time and again that "the specification is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term." *Semitool, Inc. v. Dynamic Micro Sys.*

[12] Novozymes cites to the following passages of the '031 Patent: 1:21-24; 2:61-65; 3:11-13; 3:18-23; 3:10-14; 9:5-8; 9:19-27; 10:1-3; 10:14-17; 10:36-37; 10:52-54; 11:8-11; 11: 35-36; 11:63-65; 17:18-19. (TE 100, A-7001–7040.)

*Semiconductor Equip. GmbH*, No. 05-1299, 2006 WL 871150, at *8 (Fed. Cir. Apr. 6, 2006) (citations and quotations omitted). The Federal Circuit's *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), *cert. denied*, 126 S. Ct. 1332 (2006), emphasized the "dominance of the specification in understanding the scope and defining the limits of the terms used in the claim." *On Demand Mach. Corp. v. Ingram Indus., Inc.*, No. 05-1074, 2006 WL 827302, at *4 (Fed. Cir. Mar. 31, 2006 (emphasis added)). Thus, "[i]n general, the scope and outer boundaries of claims is set by the patentee's description of his invention." *Id.*, at *5 (citing *Phillips*, 415 F.3d at 1313-14).

Flouting these rules, Novozymes ignores the most important aspects of the '031 Patent specification, those that give clear, on-point definitions of "parent *Bacillus stearothermophilus* alpha-amylase." This is wrong. The Court must consider all parts of the specification in the claim construction exercise, as the Federal Circuit's detailed analyses repeatedly emphasize and exemplify. *See, e.g., Phillips*, 415 F.3d at 1313-20; *On Demand*, 2006 WL 827302 at *4-9; *Nystrom v. TREX Co.*, 424 F.3d 1136, 1143-44 (Fed. Cir. 2005).

The law is clear – "the entire specification" must be considered in claim construction. *Amhil Enters. Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1559 (Fed. Cir. 1996.) Novozymes' construction ignores the Federal Circuit's clear rule. It should be rejected.

(c) *Novozymes' construction ignores how it characterized the asserted claims during prosecution*

It is important to remember that the asserted claims issued in fulfillment of Novozymes' "option" plan to manipulate the prosecution to obtain broad claims. Thus, Novozymes' statements during that prosecution are especially informative. Yet, Novozymes' construction improperly ignores its statements to the Examiner made when it submitted the asserted claims and demonstrated how those claims were supported in its application. (Genencor's Post-Trial Brief at 5-8; FF 135-142; CL 4-7, 12.)

In response to the Examiner's suggestion that the claimed variants should be defined by their percent homology to SEQ ID NO:3 (OA mailed April 6, 2004, at 4; TE 101 at 677, A-7717), Novozymes

presented new claim 48 (issued claim 1), reciting percent homology to a "parent" but not explicitly SEQ ID NO:3. Nevertheless, Novozymes' accompanying statements defined such "parent" as SEQ ID NO:3:

> Support for the subject matter set forth in Claims 48-52 [issued claims 1-5] is found in the specification as originally filed, including for example, the disclosures on page 10, third and fifth paragraphs (describing variants of *Bacillus stearothermophilus* and variants having at least 95% homology to SEQ ID NO:3), page 13, first and second paragraphs (describing the deletion of residues R179 and G180 in *Bacillus stearothermophilus* and SEQ ID NO:3), and page 15, lines 13-15 (describing substitutions L349C and I428C in connection with *Bacillus stearothermophilus* and SEQ ID NO:3).

Amendment, dated September 6, 2004, at 3. (TE 101 at 695, A-7735 (emphasis added).) Novozymes referred to the third and fifth paragraphs on page 10 of the specification as providing the written description required by 35 U.S.C. § 112, and characterized these paragraphs as "describing variants of *Bacillus stearothermphilus* and variants having at least 95% homology to SEQ ID NO:3" (emphasis added). Those application passages correspond to column 7:32-35 and column 7:41-51 of the '031 Patent (TE 100 at 11, col. 7:32-35, 7:41-51, A-7011), and are within the passages, quoted above, that Novozymes ignored in its construction analysis. Those passages cite specifically to SEQ ID NO:3 as the only *Bacillus stearothermophilus* parent and not to any other definition of "parent." (TE 100 at 11, col. 7:32-51, A-7011.)

Again, Novozymes ignores these passages, which contradict its hoped-for constructionbecause, during prosecution, Novozymes construed all of the asserted claims to be limited to the amino acid sequence of SEQ ID NO:3 as the "parent" against which infringement would be evaluated. (*See* Genencor's Post-Trial Brief at 5-8; FF 135-142; CL 4-7, 12.) Novozymes should not now be permitted to ignore the intrinsic record and take back the statements it made to obtain issuance of the '031 Patent. *See Nystrom*, 424 F.3d at 1145-46. Novozymes may not now rely on a broader construction of "parent *Bacillus stearothermophilus* alpha-amylase" than that it asserted to obtain the '031 Patent. *See id.*; *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 998 (Fed. Cir. 2006); *Terlep v. Brinkmann Corp.*, 418 F.3d 1379, 1385-86 (Fed. Cir. 2005).

(d) *Novozymes' construction is untenable because it is vague and indefinite*

As noted above, Novozymes' construction of "parent *Bacillus stearothermophilus* alpha-amylase" relies on "the" functional enzyme that is "actually produced" by a *Bacillus stearothermophilus* alpha-amylase gene. This construction, however, does not specify the fermentation conditions under which the alpha-amylase is produced; in fact, *different* fermentation conditions provide *different* amino acid sequences for the alpha-amylase "actually produced" by a *Bacillus stearothermophilus* alpha-amylase gene. (*See* Genencor's Post-Trial Brief at 10-11; FF 168, 170-174.) Genencor's Construction and Alternate Construction would avoid that problem, and provide fair notice of what is claimed.

Nevertheless, applying its construction to SPEZYME® Ethyl, Novozymes contends that Genencor's G-ZYME® G997 product is "the" functional enzyme that is "actually produced" by the *Bacillus stearothermophilus* alpha-amylase gene of strain G997 and, therefore, the "parent *Bacillus stearothermophilus* alpha-amylase" to which SPEZYME® Ethyl should be compared to evaluate infringement. (Novozymes' Post-Trial Brief at 10.) The problem is that Novozymes presented at trial several different amino acid sequences "actually expressed" from DNA encoding the alpha-amylase of *Bacillus stearothermophilus* strain G997. (Genencor's Post-Trial Brief at 10-11; FF 168-174.) Which of these, if any, is to be compared SPEZYME® Ethyl? Novozymes' own construction provides no guidance, and shows that Novozymes cannot meet its burden to prove literal infringement. (And, evidence introduced by Novozymes itself shows that, by its own construction, the asserted claims are invalid as indefinite under 35 U.S.C. § 112, ¶ 2. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003).)

There is neither infringement, nor valid claims, if Novozymes' construction is adopted.

(2) Novozymes' Construction Is Inconsistent With the Meaning Understood by a Protein Engineer as of 1995

Genencor has proposed its Alternate Construction in the event that the Court does not adopt its construction that "parent *Bacillus stearothermophilus* alpha-amylase" means "an alpha-amylase having the amino acid sequence of SEQ ID NO:3." (Genencor's FF 143; CL 13.) Genencor has demonstrated

that a skilled protein engineer as of 1995, considering the teachings of the '031 Patent and the published literature as of 1995, would have understood the phrase "parent *Bacillus stearothermophilus* alpha-amylase" to mean "a 514 or 515 amino acid protein encoded by a wild type *Bacillus stearothermophilus* gene, minus the signal sequence." (Genencor's Post-Trial Brief at 9-11; FF 143; CL 13.)

Novozymes insists that the "parent" must be a real, "actually expressed" protein. Genencor's Alternative Construction is based on just such a real enzyme, actually expressed.

To start with, Novozymes' expert Dr. Arnold testified that, as of 1995, a skilled protein engineer would have expected an alpha-amylase expressed from an alpha-amylase gene of a wild type *Bacillus stearothermophilus* gene to have 514 or 515 amino acids. (Arnold, Tr. at 180:1-6, A-5181.) Dr. Arnold admitted that, as of 1995, there was no evidence in the published literature of any alpha-amylase expressed from a wild type *Bacillus stearothermophilus* gene that was truncated at its C-terminus so as to have fewer amino acids. (Arnold, Tr. at 180:7-12, A-5181.) (Genencor's FF 167.)

The evidence and literature on which Genencor's Alternate Construction relies is based on studies of actual proteins, characterized by techniques ("gels") Novozymes accepts as accurate.[13] And, three pre-1995 literature publications on which Dr. Alber relied for the molecular weights of wild type alpha-amylases used alpha-amylases "actually produced" by *Bacillus stearothermophilus* alpha-amylase genes.[14] Upon reviewing the literature references on *Bacillus stearothermophilus* alpha-amylase genes

[13] Novozymes' own Dr. Jorgensen used experiments on gels to calculate molecular weights, and showed that these molecular weights were consistent with molecular weights obtained by mass spectrometry. (Alber, Tr. at 278:10-23, A-5509.) (Genencor's FF 158.) Moreover, the literature accepts such "gels" as providing an accurate molecular weight. (Alber, Tr. at 278:3-279:4, A-5509–5510.) Those skilled in the art in 1995 would have had no doubt that those pre-1995 gel experiments show correct molecular weights of the "actually expressed" alpha-amylases.

[14] Tsukagoshi *et al.* (1984) reports that the authors had purified to near homogeneity the alpha-amylase actually expressed from the alpha-amylase gene of *Bacillus stearothermophilus* strain DY-5, and had observed on a "gel" that its molecular weight was 61,000 Da. (TE 633 at 1, Summary, A-9025.) (Genencor's FF 155.) Tsukagoshi *et al.* (1985) states that the molecular weight (experimentally observed on a "gel") of the purified alpha-amylase actually expressed from the alpha-amylase gene of *Bacillus stearothermophilus* strain DY-5 is 60,000 Da. (TE 634 at 4, col. 1, A-9034.) (Genencor's FF 156.) Egelseer *et al.* (1995), reports that the molecular weight the authors obtained on a "gel" for the alpha-amylase actually expressed from the alpha-amylase gene of another *Bacillus stearothermophilus* strain, DSM 2358, is 58,000 Da. (TE 635 at 1, Abstract, A-9037.) (Genencor's FF 157.)

and on the alpha-amylases that were experimentally observed to be expressed from these genes, Dr. Alber testified that the molecular weights of the alpha-amylases are consistent with mature proteins having 514 or 515 amino acids. (Alber, Tr. 212:19-213:13, A-5213-5214.) (Genencor's Post-Trial Brief at 8-10.)

(3) The G-ZYME® G997 Product Is Not a "Parent"

Novozymes asserts, incorrectly, that SPEZYME® Ethyl should be compared in claims 1 and 5 to "the" amino acid sequence Novozymes purports to have obtained from a sample of Genencor's commercial product, G-ZYME® G997.[15] That comparison, however, is inappropriate because Genencor's G-ZYME® G997 product is not a "parent *Bacillus stearothermophilus* alpha-amylase." It has a truncation from the 515 amino acid mature protein encoded by the alpha-amylase gene of strain G997, of, variously, 27, 28, or 29 amino acids. For that reason alone, it is not a "parent *Bacillus stearothermophilus* alpha-amylase" as understood by a skilled protein engineer as of 1995, because it is not a 514 or 515 amino acid alpha-amylase. (Alber, Tr. at 249:23-250:4, A-5250–5251, 260:25-261:12, A-5261–5262.)

Second, the G-ZYME® G997 product is also not a "parent *Bacillus stearothermophilus* alpha-amylase" because it is the product of an industrial fermentation process (Alber, Tr. at 249:23-250:4, A-5250–5251, 260:25-261:12, A-5261–5262). The effects of industrial processing disqualify it from being a "parent." (Genencor's Post-Trial Brief at 10-11; FF 175-176, discussing the conditions of industrial processing and effects on proteins.)

Consequently, none of the alpha-amylases of Genencor's G-ZYME® G997 product are a "parent *Bacillus stearothermophilus* alpha-amylase" within the meaning of the '031 Patent that can be compared to SPEZYME® Ethyl to evaluate infringement of claims 1 and 5 of the '031 Patent. Rather, SPEZYME® Ethyl must be compared to either: (i) the alpha-amylase having the amino acid sequence of SEQ ID

[15] Novozymes inaccurately uses the terms "G-ZYME® G997" and "G997" interchangeably. (*See* Novozymes' Post-Trial Brief at 10 ("This same ATCC 39,709 wild-type *Bacillus stearothermophilus* alpha-amylase has also been called GZYME G997 or simply G997."), *and compare* 1, 10, and 12.) G997 is a particular strain of the *Bacillus stearothermophilus* whose alpha-amylase gene is sometimes referred to as "G997" for short. There is no dispute that G-ZYME® G997 is a commercial product, based on strain G997, but that it differs from the mature protein encoded by the alpha-amylase gene of strain G997 because G-ZYME® G997 is the product of an industrial process, and has C-terminal truncations as noted by Dr. Jorgenson and Ms. Chang. (Genencor's FF 172-177.)

NO:3, which has 514 amino acids (Genencor's Construction); or (ii) a 514 or 515 amino acid alpha-amylase encoded by a wild type *Bacillus stearothermophilus* gene, minus the signal sequence (Genencor's Alternate Construction).

C. **Novozymes' Construction of "% Homology" Is Incorrect**

There are a number of fundamental oversimplifications in Novozymes' construction of "% homology." Novozymes' attempt to construe % homology as requiring use of the GAP (GCG) program is simply wrong.

(1) Novozymes Mischaracterizes the Meaning of "% Homology"

Novozymes contends that calculating % identity answers the question, "[h]ow much of one sequence is present in the other sequence?" (Novozymes' Post-Trial Brief at 9 and 19.) This is incorrect. Percent homology answers the question, "how similar is an entire sequence to another entire sequence?" (Alber, Tr. at 235:9-236:3, A-5236–5237.) Novozymes mischaracterizes the purported purpose of calculating % homology, because this definition (falsely) supports Novozymes' argument that deletions need not be taken into account when calculating % homology. This Court should not be fooled by Novozymes' rhetorical sleight of hand.

(2) Novozymes' Construction Improperly Limits the Calculation of % Homology to the Method of the GAP (GCG) Program

Novozymes states that "[t]he GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used . . . ." (Novozymes' Post-Trial Brief at 8 (ellipsis in original).) But nothing follows the ellipsis, raising the question "may be suitably used" . . . for what? Novozymes' analysis skips the answer and proceeds to the conclusion that the GAP (GCG) program is required to calculate % homology for determining infringement of claims 1 and 5. That is not what the '031 Patent teaches.

Even grammatically, Novozymes' construction fails. "*May* suitably be used" certainly cannot mean *must* be used, as Novozymes would have it read.

In fact, the '031 Patent states that sequence alignment can be performed "via known algorithms" and that the percent homology is "revealed" from the alignment, but how the percent homology is

"revealed" is unclear. (Alber, Tr. at 233:1-21, A-5234; TE 100 at 9, col. 4:36-40, A-7009.) (Genencor's FF 186 and 191.) The '031 Patent just does not give complete instructions for calculating % homology. (Alber, Tr. at 233:1-16, A-5234.) (Genencor's Post-Trial Brief at 11-12.)

(3) Novozymes' Construction Ignores Its Own Expert's Testimony that the '031 Patent Does Not Require Use of the GAP (GCG) Program to Calculate % Homology

Novozymes' own expert, Dr. Arnold, agreed that another program may be used or the calculation of % homology may be performed by hand. (Arnold, Tr. 181:12-182:10, A-5182-5183). She further testified that other approaches to calculate % homology existed as of 1995 which might have given a different % homology than the GAP (GCG) program. (Arnold, Tr. at 181:22-24, A-5182.) (Genencor's FF 192-194.) All of Dr. Arnold's testimony on this point is ignored in Novozymes' analysis of how % homology should be calculated.

(4) Novozymes' Construction Ignores the '031 Patent's Instruction and Its Own Expert's Testimony to Count Gaps When Computing % Homology

Novozymes' analysis of the '031 Patent to determine its teachings on computing % homology totally ignores those passages that discuss the importance of deletions and the nomenclature it proposed be used to discuss them. (TE 100 at 9, col. 3:59-65, A-7009; TE 100 at 10, col. 6:36-63, A-7010.) (Genencor's Post-Trial Brief at 13-14.) Furthermore, Novozymes ignores its own expert's admission in another litigation on a patent with the same specification as the '031 Patent that one should take into account deletions in determining % homology. (Arnold, Tr. at 185:7-21, A-5186; TE 511 at 12, ¶ 30, A-8886.)

Dr. Arnold previously submitted a declaration to this Court construing "% homology" in the claims of U.S. Patent No. 6,297,038, which has the same specification as the '031 Patent (and claims different variants of SEQ ID NO:3),[16] in a litigation among Novozymes, EDC, and Enzyme Bio-Systems Ltd. (later purchased by Genencor). (TE 511, A-8875–8900.) In paragraph 30 of that declaration, she

[16] U.S. Patent No. 6,297,038 has a specification identical to that of the '031 Patent because the application that issued as the '031 Patent is a division of a continuation of the application that issued as Patent No. 6,297,038. (TE 100 at 2, A-7002, "Related U.S. Application Data.")

provided an explicit definition of % homology. (TE 511 at 12, ¶ 30, A-8886.) For the term "at least 80% homology to SEQ ID NO:3," Dr. Arnold stated that the maximum number of changes from SEQ ID NO:3 would be 103 additions, substitutions, or deletions (103 being 20% of the 514 amino acids in SEQ ID NO:3). (TE 511 at 12, ¶ 30, A-8886.) At trial, Dr. Arnold admitted that she took deletions into account in construing % homology in that other litigation:

> Q. In paragraph 30 of your declaration, Exhibit 511, you note in determining percent homology the taking into account of additions, substitutions or deletions. Do you see that? . . . . [¶] Particularly the last sentence it says. "That is, the parent would have an additional 98 additions, substitutions or deletions compared to SEC ID No. 3 in order to have less than 80 percent homology." Do you see that?
>
> A. Yes, I see that.
>
> Q. *So for purposes of your declaration in the other matter where you* worked *with Novozymes in determining percent homology, you did in fact take into account additions, substitutions or deletions; correct?*
>
> A. *I did.*

(Arnold, Tr. at 185:7-21, A-5196 (emphasis added.)) (Genencor's FF 207.)

In contrast to Novozymes' current construction of % homology, which only uses the GAP (GCG) program and ignores "deleted" amino acids of "gap" regions, Dr. Arnold clearly stated in her declaration in that prior litigation that deletions should be taken into account in calculating % homology.[17] Once again, Novozymes ignores testimony of Dr. Arnold in construing % homology.

(5) Use of the GAP (GCG) Program Alone Provides a % Homology that Is Useless to a Protein Engineer Who Needs to Know All Sequence Differences Between a Variant and Its Parent

Finally, use of the GAP (GCG) program alone is not useful to a protein engineer engaged in designing and making new proteins with improved properties. (Alber, Tr. at 235:9-236:3, A-5236–5237.) The % homology information from the GAP (GCG) program was designed for bioinformatics researchers

[17] Novozymes' attempt to defuse this testimony at trial was ineffective. It tried, through redirect examination, to distinguish the declaration paragraph in question by arguing that the paragraph related to % homology between the parent and SEQ ID NO:3 and not the variant and SEQ ID NO:3. (Arnold, Tr. at 188:13-190:3, A-5189–5191.) This "distinction" without a difference is obviously irrelevant to whether deletions should be counted in calculating % homology.

wanting to "mine" a large database of sequences to find those having the identical chosen sequence within a larger sequence—an entirely different field of research from designing and making proteins with improved properties. (Alber, Tr. at 235:22-236:3, A-5235–5236; Devereaux, Tr. at 116:10-117:7, A-5117–5118.)

None of Novozymes' arguments address the core teachings of the '031 Patent, that deletions, the very basis of patentability, must be counted in determining % homology. Genencor's Construction should be adopted.

## V. CONCLUSION

Unable to defend its actions, or even to address its own statements in prosecution, Novozymes' lawyers attempt to explain away their significance. Novozymes' approach bolsters the conclusion that it acted inequitably, because, as Professor Wigmore explains, when a party struggles mightily to explain away the significance of its fraudulent conduct, "[a] consciousness of the weakness of the cause is the natural inference." 2 Wigmore on Evidence § 281 at 131 (3d ed. 1940).

For all these reasons, and as explained in Genencor's Opening Post-Trial Brief, Genencor's Proposed Findings of Fact and Conclusions of Law should be adopted, and judgment of non-infringement, invalidity, and unenforceability of the '031 Patent should be entered against Novozymes.[18] Additionally, the many compelling bases for judgment in favor of Genencor, most especially Novozymes' inequitable conduct and the clear obviousness of the '031 Patent, also support a finding that Genencor is entitled to its attorneys fees in this exceptional case. (Genencor's CL 115-122.) *See* 35 U.S.C. § 285; *A.B. Chance Co. v. RTE Corp.*, 854 F.2d 1307, 1312 (Fed. Cir. 1988); *S.C. Johnson & Son, Inc. v. Carter-Wallace, Inc.*, 781 F.2d 198, 201 (Fed. Cir. 1986).

[18] In its Proposed Findings of Fact, Novozymes relies on three exhibits which were not admitted during trial. Specifically, Novozymes relies on TE 200 in its FF 69, TE 124 in its FF 153, and TE 184 in its FF 154. **Genencor moves to strike these findings and objects to their presentation to the Court because they rely on evidence not admitted into the record.**

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May 5, 2006

**CERTIFICATE OF SERVICE**

I, Donald E. Reid, hereby certify that on the 5th day of May, 2006 a Defendants' Opposition Post-Trial Brief was served by electronic filing upon counsel of record:

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